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REVIEW

OPEN

The pathophysiological role of portal hypertension in metabolic dysfunction–associated steatotic liver disease

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Abstract

Portal hypertension (PH) develops when static lesions such as steatosis, fibrosis, and cirrhotic nodules accumulate within the liver due to alcohol, metabolic syndrome, or other etiologies. In addition, dynamic components further enhance the hepatic vascular resistance (HVR) caused by activated hepatic stellate cells (HSCs) and sinusoidal endothelial cells (SECs). Both alcohol-associated liver disease (ALD) and metabolic dysfunction–associated steatotic liver disease (MASLD) are significant global health burdens, and knowledge on the pathophysiology behind the development of complications to PH is crucial. Hepatic cells with compromised function, such as hepatocytes, HSCs, and SECs, are deeply involved in the hemodynamic changes, impaired degradation of vasoactive substances, production of vasodilators, immune function, and mechanosensing. PH remains the main driver of liver-related complications, but it is often measured lower than expected in MASLD, partly because of the presence of inter-sinusoidal communications. The aim of this overview is to highlight pathophysiological aspects of PH in ALD and MASLD.

Keywords: cirrhosis, metabolic dysfunction–associated steatotic liver disease, mechanobiology, portal hypertension

Abbreviations: ALD, alcoholic-associated liver disease; APRI, AST to platelet ratio index; ARFI, acoustic radiation force impulse; CO, carbon monoxide; CSPH, clinically significant portal hypertension; ELF, enhanced liver fibrosis score; eNOS, endothelial nitric oxide synthase; ET, endothelin; FHVP, free hepatic venous pressure; FIB-4, fibrosis-4 index; HBF, hepatic blood flow; HVR, hepatic vascular resistance; IR, insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NAS, NAFLD Activity Score; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIT, non-invasive test; NK, natural killer; NO, nitric oxide; PH, portal hypertension; PVP, portal venous pressure; SEC, sinusoidal endothelial cell; T2DM, diabetes mellitus type 2; TE, transient elastography; TGFβ1, tumor growth factor- β1; TIMP-1, tissue inhibitor of metalloproteinase-1; TNF-α, tumor necrosis factor-α; WHVP, wedged hepatic venous pressure.

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INTRODUCTION

Portal hypertension (PH) is a common and severe complication of chronic liver disease and is responsible for the classical complications of cirrhosis, such as bleeding from gastroesophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathy, and disturbances of liver metabolism. The risk of decompensation occurs when the HVPG exceeds 10 mm Hg, which is also defined as clinically significant portal hypertension (CSPH).[1–3] CSPH is an independent predictor of the development of hepatic decompensation, liver-related complications, HCC, and mortality.[4] An increase in HVPG above 10 mm Hg is associated with a 6-fold increase in the risk of developing HCC.[5,6]

According to the anatomical location of the lesion, PH can be categorized as prehepatic, intrahepatic, or posthepatic. Intrahepatic PH can be divided into pre-sinusoidal and post-sinusoidal PH. Alcohol-associated cirrhosis is most often associated with post-sinusoidal PH, whereas inflammatory and malignant conditions can result in a pre-sinusoidal PH (Figure 1).

PH correlates with the degree of fibrosis and the size of the regeneration nodules, which particularly holds true in advanced cirrhosis, where the HVR is mediated by architectural distortion of the liver and its lobules.[7,8] In particular, the prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD) has increased during the last decades, averaging more than 25% of the Western population.[9] In asymptomatic patients with suspected chronic liver disease, it is not always possible to distinguish steatosis and fibrosis from cirrhosis despite the use of non-invasive testing (NIT), and the type and severity of the anatomical alterations may affect the risk of developing CSPH.[4,10] Different etiologies to chronic liver disease may affect the structure of the hepatic lesions and HVR differently, thereby having varying impacts on the measured portal pressure. In this review, we aim to synthesize current evidence comparing MASLD and other etiologies regarding the pathophysiology of PH.

PATHOPHYSIOLOGY OF PH

Intrahepatic PH arises in conditions associated with hepatic accumulation of lipid, fibrosis, and inflammation. The distribution and type of hepatic lesions involved in the development of PH depend on the etiology of the liver disease, where the contribution may differ between alcohol associated, viral, autoimmune, or nutritional-dependent liver diseases.[11] The level of PH depends on structural as well as on functional changes, which may vary between the individual etiologies as described below. Among the functional players are a variety of cells, microvascular changes, and the involvement of numerous vasoactive substances and activation of neurovascular systems.[12]

The hepatic vascular resistance

The HVR comprises both a dynamic and a static or structural component. The structural component consists of lesions that tend to reduce the cross-sectional area of the sinusoids, such as liver fibrosis and collagen, steatosis, regeneration nodules, capillarization of sinusoids, and vascular occlusion by thrombi.[13]

The dynamic component encompasses functional players at the cellular and vascular levels. Sinusoidal

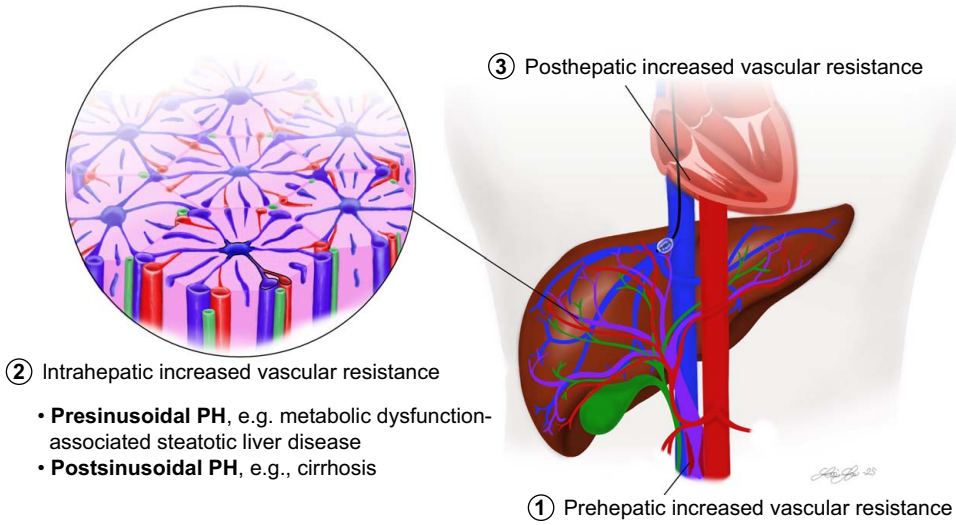
3 Posthepatic increased vascular resistance
2 Intrahepatic increased vascular resistance
• Presinusoidal PH, e.g. metabolic dysfunction-associated steatotic liver disease
• Postsinusoidal PH, e.g., cirrhosis
1 Prehepatic increased vascular resistance

FIGURE 1 Types of PH: prehepatic PH is often caused by PVT (1). Intrahepatic PH is divided into pre-sinusoidal PH, for example, caused by MASLD, and post-sinusoidal PH caused by cirrhosis (2). Posthepatic PH is most often associated with the Budd–Chiari syndrome (3).
Abbreviations: MASLD, metabolic dysfunction–associated steatotic liver disease; PH, portal hypertension.

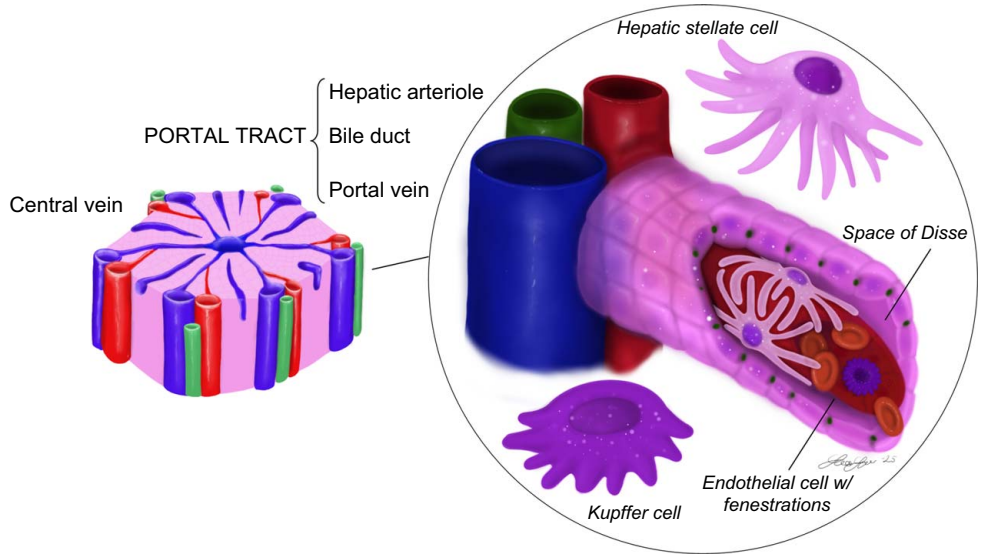

FIGURE 2 The normal liver is arranged in lobules with cords of liver cells radiating to a central vein. The portal tract consists of a triad containing a portal vein branch, a hepatic arteriole, and a bile duct. The major cells within the liver lobule are the hepatocytes and cholangiocytes, but in addition, the liver hosts hepatic sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells, which all contribute to the development of portal hypertension. The hepatic stellate cell surrounds the sinusoids in the space of Disse, and through their contractile properties, they contribute to regulating the sinusoidal blood flow.

endothelial cells (SEC) produce nitric oxide (NO), endothelins (ETs), prostanoids, and prostaglandins that act on HSCs, which possess receptors for ET-1, angiotensin-II, tissue inhibitor of metalloproteinase-1 (TIMP-1), and thrombin. HSCs surround the sinusoids in the space of Disse, and through their contractile properties, they contribute to regulating the sinusoidal blood flow (Figure 2).[12]

The normal liver is arranged in lobules with cords of liver cells radiating to a central vein. The portal tract consists of a triad containing a portal vein branch, a hepatic arteriole, and a bile duct. In addition to hepatocytes and cholangiocytes, the liver hosts SECs, HSCs, and Kupffer cells (KCs), which are important in the development of PH (Figure 2).

The hepatocytes account for ~80% of the total liver cell mass and have essential metabolic functions in terms of the synthesis of plasma proteins, regulation of carbohydrate and lipid metabolism. The hepatocytes also participate in the degradation of toxic substances, drugs, and hormones. When the liver is exposed to alcohol, hepatitis B or C virus, or excess nutritional supply, steatosis and fibrogenesis increase with impairment of hepatocyte function.[14,15]

KCs are liver macrophages and account for 15% of the liver cells. The KCs are important for the immune function of the liver and act as antigen-presenting cells for bacteria, endotoxins, lipopolysaccharide, and other antigens together with natural killer (NK) cells.[16] In addition, the KCs play an important role in the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 and interleukin-6 (IL). Furthermore, KCs play important roles in the clearance of endotoxins, and in the defense of microbial infections and contribute to the production of NO.[17]

HSCs are in the space of Disse in close contact with hepatocytes and SEC (Figure 2). In PH, activated HSCs are dynamically involved in the production of extracellular matrix and collagen, leading to enhanced fibrogenesis and matrix degradation, where TIMP-1 has been shown to be a survival factor for HSC.[13,18] In addition, HSCs exert an important contractile action surrounding the sinusoids in the space of Disse as an essential element of the dynamic HVR of PH (Figure 2).[19–21] Liver injury, oxidative stress, and inflammation stimulate production of VEGF from the HSC, eliciting endothelial NO synthase (eNOS) activation and NO production from the SEC.[13] Because of endothelial dysfunction, there is a lack of hepatic NO production in PH,[22] which results in a contractile state within the liver. Together with the simultaneous production of potent vasoconstrictors such as ET-1, noradrenaline, AT-II, and thromboxane-A2 from SEC acting on the activated HSC, a preferential contraction is the result, reducing the sinusoidal vascular diameter.[13,21] From this point of view, the contraction of HSC constitutes a reversible and dynamic component of the increase in hepatic blood flow (HBF) and regulation of the portal pressure. In addition, the HSCs cover various physiological functions, including activation of the immune response, secretion of cytokines, and angiogenesis. The inflammatory response plays an important role in fibrogenesis since inflammation always precedes fibrosis, and immune activation induced by bacterial lipopolysaccharides induces

fibrosis.[12,23] KCs also activate HSC by increased nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity and secretion of pro-inflammatory cytokines, including TNF-α and monocyte chemoattractant protein.[24] Finally, NK cells have an anti-fibrotic effect by killing activated HSC. The contractile HSC contributes to the regulation of the sinusoidal blood flow and to angiogenesis in the cirrhotic liver.[21] Together with SECs that exert a paracrine effect through NO synthesis, the HSCs represent an important dynamic component of the sinusoidal hemodynamic resistance in cirrhosis.

Fibrogenesis

Sustained fibrogenesis is a hallmark of most chronic liver diseases, characterized by distortion of the liver parenchyma and reduction of the vascular architecture. Like activation of hepatic cells, this process can be activated and perpetuated by alcohol, HBV and HCV, excessive nutritional intake, and metabolic changes. Such stimuli primarily activate HSC into myofibroblast-like cells with contractile, proliferative, and fibrogenic capacities, and it is the primary cell type responsible for deposition of extracellular matrix in the liver.[25,26] The HSCs lie in the subendothelial space between the hepatocytes, KCs, and SECs, so they mutually interact through numerous cellular processes extending across the space of Disse (Figure 2).[27,28] Paracrine and autocrine activation of HSCs by tumor growth factor-β1 (TGFβ1), which is considered the most potent fibrogenic cytokine, initiates the fibrotic process in the liver.[21]

The splanchnic and HBF

The liver receives 25% of the total resting cardiac output through the hepatic artery and portal vein, the latter being responsible for 75% of the total HBF. HBF is regulated by the hepatic arterial buffer response, and in case of PH with high HVR and splanchnic vasodilatation, the hepatic artery is maximally dilated.[29] In PH, HBF increases because of splanchnic vasodilatation due to VEGF-induced eNOS production of NO from SEC and VEGF-driven angiogenesis that contributes to the development of porto-systemic collaterals.[13,21] Other vasodilators such as carbon monoxide (CO), glucagon, and endocannabinoids may, in addition to bacterial translocation, where bacteria or bacterial products activate eNOS, further aggravate the splanchnic vasodilatation.[23] There are no mechanisms within the liver to control the portal inflow, and therefore, different regulatory mechanisms are essential to maintain hemodynamic homeostasis. The hepatic arterial buffer response is mentioned above. According to this hypothesis, a reduction in portal blood flow will cause a local accumulation of adenosine, not washed away from the space of Mall surrounding the hepatic arterial resistance vessels, and this will lead to local vasodilatation.[29]

Mechanobiology

Mechanotransduction is a relatively new discipline in the understanding of the pathophysiology of PH. It seeks to describe how mechanical signals through mechanosensing and mechanotransmission elicit a mechanoresponse.[12] By means of complex biomolecular cascades, mechanical cues contribute to the pathogenesis of PH.[30] Mechanotransduction can be defined as a process where cells such as hepatocytes, HSCs, and SECs sense physical signals that elicit a response.[30] Because SECs exist in a low-pressure zone, an absolute change of more than 5 mm Hg is sufficient to induce CSPH.[20,31] Hence, even a relatively low change in sinusoidal pressure increases the response to steatosis, inflammation, and angiogenesis even in the absence of fibrosis.[32] This concept is of special interest in MASLD and supports a bidirectional pathogenic relationship between sinusoidal pressure and fibrosis, in part mediated through mechanosignalling.

Mechanosensing

The primary pathophysiological changes in MASLD include fat accumulation as steatosis and ballooning, HSC trans-differentiation with extracellular matrix expansion, activation of the inflammatory response, and endothelial dysfunction. Massive fat accumulation in the hepatocytes induces an internal cellular compression with impaired albumin synthesis, glycogen storage, and proliferation, as well as an external compression and constriction of the sinusoids by activated HSC (Figure 3).[33] Production of extracellular matrix by the activated HSC impairs the hepatocyte function, causing accumulation of extracellular matrix that compresses and stretches not only the hepatocytes, but also affects sinusoidal blood flow by inducing turbulence.[34] Shear stress exerts a tangential force on the SECs, which are the primary sensors of flow, stretch, and pressure changes.[30] SECs are fenestrated and lack a basal membrane that allows bidirectional transport of small substrates between the sinusoids and the space of Disse (Figure 3).[35] In MASLD, shear stress is an important cue for the mechanoresponse in SECs, which includes progressive loss of the fenestrated endothelium, capillarization with formation of basement membrane, and endothelial dysfunction with impaired NO production and enhanced VEGF-receptor presentation as key features.[35–37]

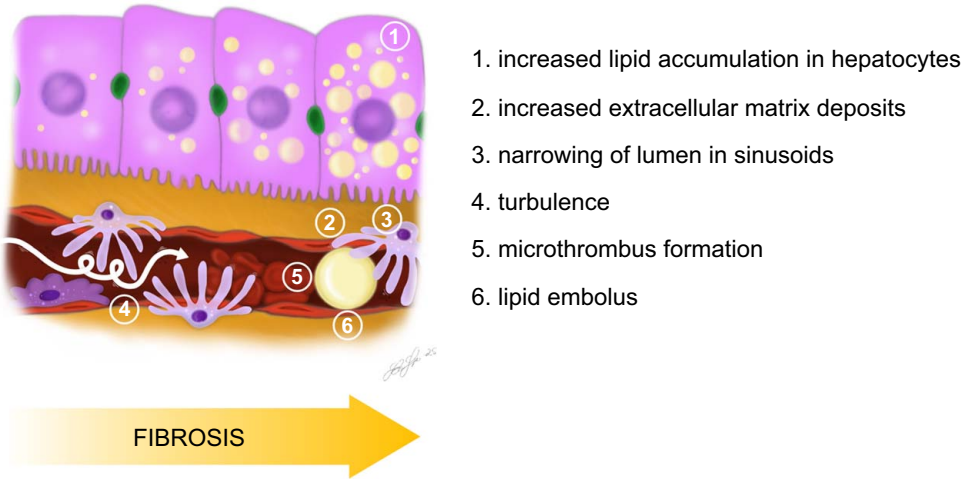

FIGURE 3 Mechanobiology describes how mechanical signals through mechanosensing and mechanotransmission elicit a mechanoresponse. Fat accumulation in the hepatocytes induces an internal cellular compression (1). Production of extracellular matrix (2) by the activated HSC compresses and stretches the hepatocytes and narrows the lumen of the sinusoids (3), causing turbulence (4). Presence of microthrombi (5) and lipid emboli (6) further enhances this process by exerting a tangential force on the sinusoidal endothelial cells, which are the primary sensors of flow, stretch, and pressure changes.

Decreased bioavailability of NO leads to disruption of NO-mediated vasoregulatory responses, including loss of inhibitory control over HSC.[38]

PATHOPHYSIOLOGY OF MASLD

Briefly, MASLD covers a wide range of pathological phenotypes with inflammation, metabolic dysfunction–associated steatohepatitis (MASH), increasing stages of fibrosis (stage 0–3), and cirrhosis. Typically, lipids are initially stored in hepatocytes around the central vein, described as zone 3, but with the progression of the disease, all zones become involved. The morphology of steatosis is divided into macrovesicular or microvesicular, dependent on the size of the lipid droplets, although this pattern does not discriminate between etiologies. The combination of steatosis, inflammation and swelling of the hepatocytes owing to injury, termed ballooning, is required for the diagnosis of steatohepatitis.[39,40] It is characteristic of steatotic liver disease that it begins near the central vein at zone 3 hepatocytes. According to the histologic scoring system, NAFLD Activity Score (NAS) stages 1a and 1b comprise pericellular and periportal (1c) fibrosis. Stage 2 pericellular and periportal fibrosis, stage 3 bridging fibrosis, and stage 4 cirrhosis.[39]

Excess nutrition is the main driver in the development of MASLD, which is thought to be a manifestation of the metabolic syndrome, but variable comorbid, genetic, and environmental factors also play differential roles in the progression of MASLD to MASH.[41]

Mechanisms of particular importance in the pathophysiology of MASLD are insulin resistance (IR), dyslipidemia, gut dysbiosis, and genetic risk factors.[9] Several cross-sectional and prospective studies have substantiated this. In a cohort of 213 healthy individuals, 66 patients had MASLD at baseline, and 19% developed MASLD within 7 years and baseline IR and weight gain turned out to be the strongest predictors of MASLD.[42] Of importance is that progression from steatosis to MASH with significant fibrosis seems to be more prevalent in patients with type 2 diabetes mellitus (T2DM).[43,44] However, it is still an enigma why it is only a smaller fraction of MASLD patients that progress to MASH and why only a minority of MASH patients develop cirrhosis. Gut microbiota dysbiosis has been seen in patients with metabolic syndrome, obesity, and T2DM, as well as in MASLD.[45,46] Different pathogenic mechanisms have been proposed, such as defective barrier function, inflammation, and microbial ethanol production.[47,48] Finally, genome-wide association studies (GWAS) have identified polymorphisms, which affect the risk of MASLD, including *PNPLA3*, *TM6SF2*, *MBOAT7*, *GCKR*, and *HSD17B13*.[49–51] Polygenic risk scores may predict the risk of MASLD development and progression as well as the development of cardiovascular disease.[49,52,53]

Knowledge of the pathophysiological mechanisms may introduce new therapeutic strategies for PH in MASLD, where endothelial dysfunction, inflammation, and fibrogenesis are pertinent targets.[22] Endothelial dysfunction is characterized by impaired NO bioavailability, increased oxidative stress, and pro-inflammatory cytokine production and is a key driver of fibrogenesis.[15] This points to anti-inflammatory drugs such as perioxisome proliferator-activated receptor agonists, such as pioglitazones and lanifibranor, caspase inhibitors, and IL-1 and TNF-α inhibitors.[54] Anti-fibrotic drugs include galectin-3 inhibitors and fibroblast growth factor analogs, whereas NO-enhancing therapies relate to, for example, eNOS-

activators and phosphodiesterase-5 inhibitors.[21,55] Currently, several randomized controlled trials seek to evaluate the effects of these drugs on MASLD.

PH IN MASLD

It is a major challenge that measurement of the HVPG in MASLD has a lower accuracy primarily because of persistence of inter-sinusoidal channels.[28] Although present in the normal liver these sinusoidal communications seem most pronounced in steatosis and in milder degree of fibrosis, but may disappear in the cirrhotic stage because of obstruction by the cirrhotic scar tissue.[32] Patients with MASLD present a higher rate of PH-related decompensation at any given HVPG value as compared with patients with chronic liver disease of other etiologies. This is most likely explained by the underestimation of the real portal pressure gradient in MASLD.[56]

PH and severity of MASLD

The portal pressure gradient begins to rise early in MASLD, and fibrosis per se is not a prerequisite for the development of PH. Accordingly, the HVR begins to increase because of reduced sinusoidal space for several reasons. Approximately 25% of the HVR is attributed to functional changes relating to SEC and HSC, and 75% of the HVR to structural changes such as lipid droplets, fibrosis, thrombi, and regeneration nodules seen in advanced stages of MASLD[12,57] (Figure 3). In early MASLD, the increase in HVPG often precedes fibrosis and is initiated by mechanoresponses from compression, shear stress, and stretch from the steatotic hepatocytes and ballooning, leading to a reduced sinusoidal space and compromised HBF.[34] Further activation of SEC and HSC by mechanoresponses may induce fibrogenesis and a further increase in the HVPG as a bidirectional mechanism. This has been supported by clinical studies in obese patients with suspected MASLD, where the degree of steatosis was the only independent predictor of PH in the absence of fibrosis.[58,59] PH can occur in a small proportion of MASLD patients without fibrosis and is associated with the extent of steatosis.[60] In a larger retrospective study, patients with ALD had a higher level of PH than patients with MASLD and other etiologies.[61] Also, visceral adiposity and IR seem to predict hepatic steatosis and PH in MASLD patients and may help to identify patients at risk.[62]

Signs of PH are present in 25% of MASH patients, correlating with the degree of fibrosis and development of complications.[60] However, patients with CSPH and signs of advanced liver disease do not necessarily have cirrhosis[63] and patients with MASH do not have severe PH in the absence of cirrhosis.[64]

In obese patients with MASH and compensated chronic liver disease, the prevalence of PH is lower than in other etiologies.[65,66] In MASH a disturbed levels of pro-inflammatory markers are involved in the histological processes leading to increased PH.[59]

The accuracy of HVPG measurements depends on the type of PH. For example, in the case of prehepatic PH induced by a portal vein thrombosis, HVR is presinusoidal and “pre-thrombotic” and the “pre-thrombotic” portal venous pressure (PVP) is increased while the “post-thrombotic” PVP appears normal, wherefore the “pre-thrombotic” PVP significantly exceeds the wedged hepatic venous pressure (WHVP) (Figure 4A). The lesions that cause PH in MASLD-cirrhosis and those seen in cirrhosis caused by alcohol or HCV are also different, and the type of PH depends on the site and type of histopathological changes (Figure 4B).

PH is the main driver of hepatic decompensation in advanced liver disease, but the hemodynamic impact of MASLD on portal pressure is discussed.[32,63,67] The gold standard of assessing CSPH in MASLD is to measure the HVPG as the difference between the WHVP and free hepatic venous pressure (FHVP).[68] CSPH is often present in F3 stages and in cirrhosis; some studies have shown low or normal HVPG in pure steatosis and in F0 and even in F3 stages.[64,69] An important contributing factor for the relatively lower measured PVP in MASLD may be the presence of more intrahepatic shunts and inter-sinusoidal channels than in other liver diseases, as shown in Figure 4C.[30,70,71]

Other factors of importance may relate to a differential extent of endothelial dysfunction and architectural differences of the type and histological site of fibrosis. In MASLD, the actual PVP may be underestimated, and the HVPG appears to be ~4 mm Hg lower than in patients with other etiologies of cirrhosis, such as those induced by HCV, which should be taken into consideration in the interpretation of the severity of PH in MASLD patients.[56,72] Despite this, there seems to be a strong correlation between HVPG and stage of fibrosis in MASLD.[66]

In general, portal pressure measurements are lower in MASLD patients compared with what should be expected from their clinical phenotype and severity of complications. This has been confirmed in a recent prospective study in patients with MASH-cirrhosis and cirrhosis of other etiologies who underwent TIPS with direct measurements of portal pressure compared with the WHVP.[73] The correlation between PVP and WHVP disagreed in patients with MASH-induced cirrhosis, with WHVP measurements underestimating PVP in MASLD. This calls for a discussion of a lower threshold of HVPG in MASLD. In a large prospective trial, an HVPG threshold ≥ 10 mm Hg predicted decompensation in NASH-cirrhosis, but in a 5-month period, decompensation also developed in a subset of patients (14%) with HVPG < 10 mm Hg.[74] Somewhat similar results were obtained in a large multicenter study of 548 advanced MASLD patients compared with 444 advanced

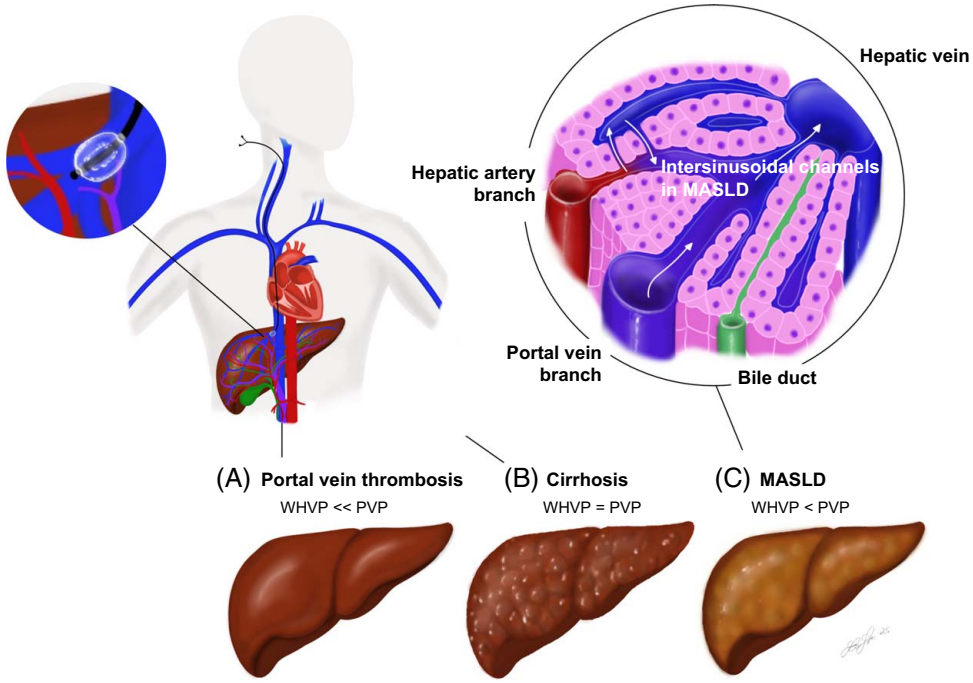

FIGURE 4 Challenges of measuring the WHVP in different conditions. In prehepatic PH and portal vein thrombosis, the measured (lower) WHVP is not representative of the actual PVP (A). In this case, "the pre-thrombotic pressure" exceeds "the post-thrombotic pressure." In cirrhosis, inter-sinusoidal channels are blocked, leading to equally measured PVP and HVPG (B). In advanced MASLD, persistent inter-sinusoidal communications reduce the accuracy of the WHVP in estimating the PVP. $<<$ means WHVP is much less than PVP. $<$ means WHVP is less than PVP. Abbreviations: PH, portal hypertension; PVP, portal venous pressure; MASLD, metabolic dysfunction–associated steatotic liver disease; WHVP, wedged hepatic venous pressure.

HCV patients.[56] In this study, MASLD patients had a higher prevalence of decompensation at any HVPG value than HCV patients. The predictive value of the HVPG measurement may also depend on the severity of the disease. In a recent European multicenter study of 340 compensated MASLD advanced chronic liver disease patients, HVPG measurement proved a high prognostic value and in MASLD patients without CSPH the short-term risk of decompensation and liver-related mortality were low.[4] Nevertheless, HVPG-based prediction of decompensation in MASLD is less reliable in particularly in less advanced MASLD and another threshold to predict decompensation and long-term outcomes in MASLD patients is warranted. From a clinical point of view, low values of HVPG of ~4 mm Hg should be interpreted cautiously in MASLD patients with advanced steatosis/fibrosis. Moderately increased HVPG values from 9 to 10 mm Hg should lead to closer surveillance with potential revision of risk factors.

DIAGNOSIS OF PH

Measurement of the HVPG by hepatic venous catheterization remains the gold standard in the assessment of PH.[75,76] The HVPG is assessed as the difference between the free and the WHVP. In posthepatic or post-sinusoidal cirrhosis, HVPH is often 1–2 mm Hg lower than the PVP. In patients with prehepatic or pre-sinusoidal PH, for example, in the case of a portal venous thrombi, the HVPG does not reflect the true portal pressure (Figure 4).[77]

Assessment of HVPG is the current preferred technique for determining portal pressure and is a validated surrogate outcome measure in the prognosis of PH, with a consistent association with the clinical outcomes in chronic liver disease.[5,76] Assessment of PH is essential in the accurate diagnosis of PH and assessment of prognostics in patients with cirrhosis, although a differential lower threshold seems relevant with respect to the prediction of outcomes in MASLD. It should be brought to mind that MASLD covers the entire span of the disease from early pre-sinusoidal PH to advanced sinusoidal PH. It is therefore important to differentiate the individual stages of the disease in relation to the type and level of PH.

Measuring HVPG can be performed through various venous access points, most often the jugular, femoral, or antecubital veins, using either the balloon catheter method or the end-hole method.[78] The hepatic vein is catheterized by x-ray guidance, and the location is verified using an infused contrast medium. The catheter is connected to a pressure monitor with characteristics that allow dynamic recordings of the pressure variation. FHVP is measured with the placement of the catheter in a large liver vein. Using a balloon catheter, the balloon is insufflated, thereby occluding the liver vein, and the WHVP can be measured.

When the hepatic vein is occluded, the hepatic venous outflow is blocked, forming a continuous column of fluid between the catheter and the sinusoids equal to the sinusoidal pressure and the WHVP (see Figure 4). In cirrhosis, the inter-sinusoidal connections are blocked, meaning there will be no dissipation of the pressure, and the static column of blood in the hepatic vein where the catheter is placed, extends all the way to the portal vein.[77]

Measurements of the portal pressure are important to assess the degree of PH and presence of CSPH, since the risk of clinical decompensation increases by 11% for each 1 mm Hg increase in HVPG.[5] This means that, for example, having a baseline HVPG of 15 mm Hg, the risk of developing decompensation is 55% higher compared with a patient with an HVPG of 10 mm Hg at comparable MELD score.

In patients with compensated cirrhosis, an HVPG above 10 mm Hg is a significant predictor of the development of variceal bleeding, which only develops at HVPG >10 mm Hg and a HVPG below 12 mm Hg indicates little or no risk of variceal bleeding.[1,76,79] HVPG measurement is also a robust predictor of clinical decompensation besides variceal bleeding, such as hepatic encephalopathy, ascites, and death. Thus, patients with a HVPG <10 mm Hg have a 90% chance of avoiding decompensation over the next 4 years.[5] Finally, a HVPG >10 mm Hg is an independent predictor of HCC development with a 6-fold increase in the risk of HCC and may, in addition, be valuable in determining possible outcome after surgical resection of HCC.[80]

NITs for PH

In addition to the invasive liver vein catheterization for assessment of PH, a number of surrogate makers and methods have been introduced and will be mentioned only briefly (Table 1).

TABLE 1 Non-invasive quantitative imaging and biochemical markers for the diagnosis of MASLD according to clinical performance and diagnostic accuracy

Liver fat
MRI proton density fat fraction (R, **)
Ultrasound vibration-controlled transient elastography (C, *)
Fibrosis
MR elastography (R, **)
Ultrasound elastography (C, **)
T1-weighted imaging (R, **)
Fibrosis-4 index (C, **)
Pro-C3 (C, **)
Enhanced liver fibrosis score (C, *)
Fibrotest (C, *)

Note: (R) and (C) denote whether the method is preferred for research or clinical diagnostics purposes, respectively. *Indicates low to moderate diagnostic accuracy, and **indicates high diagnostic accuracy of a marker.
Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

A variety of biomarkers are validated for the diagnosis of fibrosis. Both indirect scores with markers of liver function, AST to platelet ratio index (APRI), fibrosis-4 index (FIB-4), and platelet count together with direct serum extracellular matrix components and intermediates of fibrogenesis such as the enhanced liver fibrosis test (ELF-test) and FibroTest.[81,82] Their accuracy is reasonable to distinguish between the absence of or mild fibrosis and advanced stages of fibrosis.[83] In particular MASLD fibrosis score is useful in screening for fibrosis in MASLD patients.[84]

Liver ultrasound elastography is a technology sensitive to tissue stiffness, and the method takes advantage of the changed elasticity of the soft tissue resulting from pathological processes, as when fibrosis accumulates in the liver.[82,85] Different elastography techniques have emerged, and they can be divided according to excitation source, imaging modality, and property displayed. These techniques include transient elastography (TE), acoustic radiation force impulse (ARFI), and others.[86] TE is a patient friendly and safe technique and has extensively been evaluated and is broadly implemented in daily clinical practice.[1] TE relates to PH and its complications and allows for rapid risk stratification for patients needing further investigations, but does not quantify the severity of PH.[81] One of the major limitations of TE in clinical practice is the limited reliability in patients with obesity and ascites, and TE may therefore be less suited for some MASLD patients.[10] MR-elastography provides the ability to analyze an entire organ, and both liver stiffness and spleen stiffness measured by MR-elastography correlate with the degree of PH and severity of cirrhosis.[87] The applicability in obese patients or patients with severe ascites is good. Liver and spleen measurements perform equally well in detecting CSPH, but the modality is time-consuming and costly compared with ultrasound elastography, and it is not yet validated in large cohorts.

DIAGNOSIS OF MASLD

The gold standard for diagnosing MASLD is histological assessment with a detailed evaluation of fibrosis.[88–91] The combination of NITs is useful for the identification of patients who require a liver biopsy and therefore assessment of fibrosis is important.[9,92] The most commonly applied NITs and imaging biomarkers are summarized in Table 1.

These tests include the FIB-4 test, pro-C3, ELF, and the FibroTest.[90,92,93] Such NITs can be used together with imaging biomarkers as abdominal ultrasound, which is often used as a diagnostic tool for the assessment of hepatic steatosis[91,94] and ultrasound elastography, MR elastography, and transient elastography for diagnosing fibrosis.[95,96] MR elastography is the most accurate

imaging method for quantifying fibrosis, but the technique is expensive and less available.[96]

SUMMARY AND CONCLUSION

MASLD increasingly represents a global health burden, which now affects more than a quarter of the adult population worldwide. A considerable number will develop MASH, fibrosis, and cirrhosis and hence, PH. Hepatic cells with compromised function, such as hepatocytes, HSCs and SECs, are deeply involved in the hemodynamic changes, impaired degradation of vasoactive substances, production of vasodilators, immune function, and mechanosensing. This contributes to the pathophysiology of PH in MASLD, characterized by massive steatosis and variable stages of fibrosis and cirrhosis. In MASLD, fibrosis may, as a structural component, induce PH, whereas PH, on the other hand, may induce fibrogenesis in a vicious cycle. PH is the main driver in the prediction of liver-related complications, but is likely underestimated partly because of the presence of inter-sinusoidal communications. A major gap in our knowledge of the pathophysiology of MASLD relates to the discrepancy between histological and imaging-based evaluation and severity and portal pressure levels. Therefore, future research should focus on factors that affect the portal pressure. Visualization and quantification of inter-sinusoidal communications, for example, by use of contrast dyes, would bring us a great step further in our understanding of the portal pressure changes in MASLD. HVPG-based prediction in less advanced MASLD calls for validation of MASLD-specific thresholds to predict decompensation and long-term outcomes in MASLD patients. The interplay between endothelial dysfunction, chronic inflammation, and fibrosis in MASLD underscores the need for multi-targeted therapeutic strategies. Although trials are ongoing, we still need knowledge on how these treatment strategies may halt the disease progression, reverse fibrosis, and reduce PH. Most likely, combination therapies may offer the most promising outcomes for patients with advanced disease stages.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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